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Review

Bone marrow contributions to fibrosis ☆

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ABSTRACT

Bone marrow transplant experiments in mice using labelled donor bone marrow have indicated that following injury bone marrow derived cells can circulate and home to the injured organs. In particular fibrocytes and myofibroblasts are capable of contributing to the wound healing response, including collagen deposition. In chronic injury this can lead to a pathological degree of fibrosis. Experiments have shown that this can be a relatively insignificant contribution to the scar forming population in certain organs and that the majority of the scar forming cells are intrinsic to the organ. Conversely, in certain circumstances, the circulating cells become major players in the organs fibrotic response. Whilst cell tracking experiments are relatively simple to perform, to actually determine a functional contribution to a fibrotic response more sophisticated approaches are required. This can include the use of bone marrow transplantation from recipients with collagen reporter systems which gives a read out of bone marrow derived cells that are transcriptional active for collagen production in a damaged organ. Another technique is to use bone marrow transplants from donors that have a mutation in the collagen to demonstrate a functional difference in fibrosis when bone marrow transplants performed. Recent reports have identified factors mediating recruitment of circulating fibrocytes to injured organs, such as CXCL12 and CXCL16 and shown that blocking these factors reduced fibrocyte recruitment and subsequent fibrosis. The identification of such factors may enable the development of novel therapies to block further fibrocyte engraftment and fibrosis in situations of pathological scarring. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. General considerations—what techniques are used to assess the evidence for the bone marrow (BM) contributing to organ fibrosis?

In this section we will discuss the evidence for BM derived cells contributing to organ fibrosis. To understand the techniques that have been used to assess contribution of BM derived cells to fibrogenesis in injured organs it is worth briefly reviewing the stem cell composition of the BM.

2. The composition of the BM

2.1. The haematopoietic stem cells

The haematopoietic stem cells (HSCs) residing within the BM are multipotent and are the source of the myeloid and lymphoid populations of the blood. Haematopoietic stem cells are radiation sensitive and therefore can be studied accurately using a protocol in mice of lethal irradiation which ablates the endogenous haematopoietic stem cells, followed by injection of haematopoietic cells that are labelled or traceable in some manner. This can be through the use of genetically marked BM such as green fluorescent protein (GFP) labelled BM, sex-chromosome markers (where the recipient mice are female, XX and the donors male, XY) or other technologies. The donor haematopoietic stem cells can be purified and sorted with specific markers, following peripheral vein injection are able to engraft the irradiated recipients BM and then differentiate into the progeny of haematopoietic stem cells providing long term repopulation of all the blood lineages. The application of known doses of irradiation can produce recipient BM where practically all of the haematopoietic system is of donor origin and this can be easily checked using FACS (e.g. for GFP). Analysis of the engraftment and functional effects of the progeny of haematopoietic stem cells in injured organs is therefore relatively straightforward.

Abbreviations: BM, bone marrow; CP, chronic pancreatitis; (EOG-EPC)s, early outgrowth endothelial progenitor cells; GFP, green fluorescent protein; hSAP, human serum amyloid protein; (LOG-EPC)s, late outgrowth endothelial progenitor cells; MSCs, mesenchymal stem cells; HSCs, haematopoietic stem cells; EPCs, endothelial progenitor cells; ARDS, acute respiratory distress syndrome; NASH, non-alcoholic steatohepatitis; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; AMD, age related macular degeneration; FSGS, focal segmental glomerulosclerosis

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2.2. Fibrocytes

Fibrocytes are inactive precursors of the collagen secreting fibroblasts. Circulating fibrocytes have been identified in the blood that are CD34+, CD45+, collagen-1+. These fibrocytes are thought to be able to circulate in the blood, differentiate into fibroblasts and contribute to collagen accumulation in injured organs [1]. Fibrocytes have been implicated in fibrogenesis in the skin, lung, liver and kidney and are characterised as expressing haematopoietic markers (CD11b, GR1, CD45) as well as markers of cell adhesion (CD54) and co-stimulatory molecules CD80 and CD86 and secrete pro-fibrotic cytokines and growth factors (TGF-b and MCP-1). Fibrocytes are recruited to injured organs via a variety of cytokines and chemokines and recruitment can be inhibited in mice deficient in chemokine receptors particularly CCR2, CXCR4 and CCR5 in the lung [2,3] and CCR2, CCR7 and CXCR4 in the kidney [4]. Human serum amyloid protein (hSAP) is a natural inhibitor of fibrocyte differentiation and maturation [5]. Mice treated with hSAP develop less fibrosis in response to injury in several organs and have been successfully tested in limited clinical trials in patients with skin, kidney and lung fibrosis [6–10], suggesting an important role for these cells in pan-organ fibrosis.

2.3. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are capable of tri-lineage differentiation into osteoblasts, chondrocytes, and adipocytes [11]. MSCs are classified by the expression of mesenchymal markers CD105, CD90 and CD73, and lack of expression of haematopoietic markers CD45, CD34, CD14 and CD11b and are thus distinct from fibrocytes which express CD45 and CD11b. As well as their regeneration effects, MSCs are also thought to modulate disease progression via their anti-inflammatory and immune-modulatory properties and secrete a variety of mediators such as TGF-β, IL-10, prostaglandins and indolamine 2, 3-dioxegenase and support the development of regulatory T cells [11–15]. In addition the effects and functional properties of MSCs may be influenced by the inflammatory milieu and can adopt a pro-inflammatory MSC1 and anti-inflammatory MSC2 phenotype, similar to that adopted by macrophages [16]. Several studies have reported that MSCs from patients exhibit a completely recipient profile after total body irradiation and BM transplantation, whereas HSCs are of donor origin [17,18] suggesting that MSCs in their niches are likely to be radio-resistant. Furthermore in the experimental setting, when using standard irradiation and BM transplant procedures in mice and rats, the resident promising population is unaffected by irradiation, unlike the HSC population which becomes of donor origin. Therefore it is not straightforward to determine whether MSCs contribute to organ fibrosis in disease states. It is worth considering their fibrogenic potential either in disease, or perhaps of more relevance, following the injection of exogenous MSCs as these cells are being considered for use in cell therapies in a number of diseases. The ability to isolate and expand human MSCs in culture has stimulated research into their therapeutic potential where MSCs have been expanded in culture and injected during injury models. For example MSCs have been shown to reduce fibrosis and tubular atrophy in a rat kidney allograft model [19] and have beneficial effect in myocardial infarction, lung fibrosis and acute liver injury [20–22]. Thus MSCs may have potential clinical use in certain disease scenarios. The factors regulating the mobilisation of MSCs from the BM are less well understood than those factors governing HSC mobilisation. While GCSF stimulates MSC proliferation in the BM it does not stimulate mobilisation and a combination of the CXCR4 antagonist AMD3100 (which effectively mobilises HSCs) with GCSF did not mobilise MSCs [23] However, stromal progenitor cells have been mobilised from the BM in mice using a combination of CXCR4 and VEGF [23]. MSCs are currently being evaluated in several clinical trials for a variety of diseases, including Crohn's disease, multiple sclerosis, diabetes mellitus, and acute graft-vs-host disease, with some efficacy [11,24–26] but their use in fibrotic disease remains to be established.

3. Endothelial progenitor cells (EPCs)

EPCs are a population of mononuclear cells in the blood thought to be capable of differentiating into endothelial cells in vitro. These cells are suggested to contribute to angiogenesis either by directly differentiating into endothelial cells or by secreting proangiogenic factors and chemokines such as VEGF, CXCL12 and IGF-1 [27]. EPCs are cultured from blood mononuclear cells and form colonies in the presence of endothelial growth factors. Early outgrowth EPCs (EOG-EPC)s have characteristics of both endothelial and monocytic cells and express CD45, CD11c, and CD14, and the endothelial markers CD31 and VEGFreceptor-2. Late outgrowth EPCs (LOG-EPC)s express the endothelial markers and CD34 but do not express monocytic markers. The potential for EPC transplantation and therapy has been most widely studied in cardiovascular disease where transplantation of EPCs has been shown to reduce fibrosis in several models e.g. myocardial infarction [28]. However EPCs have also been shown to reverse liver fibrosis [29] and reduce portal hypertension associated with CCl_4-induced liver cirrhosis [30] and reduce obstructive renal fibrosis [31].

3.1. Tracking BM cells in human tissue

In humans, to determine the presence of BM derived cells in injured organs it has been necessary to analyse tissue from patients that have received BM transplants. Typically this has been female (XX chromosomes) patients that have received male (XY chromosomes) BM transplants where the Y chromosome denotes a human cell that can be tracked in a damaged organ using in situ hybridisation for the Y chromosome. This can be combined with immunohistochemistry for a cell type marker (e.g. such as αSMA to mark a myofibroblast) to confirm cell phenotype [32]. However, the combination of standard in situ hybridisation with immunohistochemistry analysis may not be sufficient to localise the nuclear Y chromosome in the nucleus with αSMA expression in the cytoplasm in individual cells [33]. Other approaches have involved analysing female organs that have been transplanted into male recipients for evidence of male (recipient) myofibroblasts in the organ, although this does not directly prove BM origin. These histological studies have been useful for suggesting a potential role of the BM in organ fibrosis but are of course descriptive and not functional. Furthermore, techniques such as in situ hybridization can be difficult to optimise and also need rigorous analysis with appropriate controls to prevent inappropriate conclusions being reached.

3.2. Evidence that the BM cells are synthesising and secreting collagen

The evidence that BM cells are synthesising collagen can be obtained using transgenic mice that are transcriptional reactive for collagen or express a fluorescent gene under the control of a specific promoter such as a collagen or αSMA gene [34,35]. However it is worth noting on a technical level that if one uses collagen reporter mice, this will show transcriptional activity at the time of assay (typically when tissue is harvested unless whole body live imaging is used). This may miss an earlier burst of transcriptional activity, furthermore collagen gene transcription is only part of the process required to actually deposit collagen in tissue. Another way of determining transcriptional activity for collagen is to look for RNA using collagen ribo-probes in cells that can be detected in tissue sections [36]. Using these approaches it has been shown that a small proportion of BM derived myofibroblasts in the liver are transcriptionally active for collagen. Another approach has used *in vivo* imaging to track collagen expressing fibrocytes to the liver using BM from chimeric mice expressing luciferase under control of the α1(I) collagen promoter [37]. Another study used BM transplantation from donor mice with a genetic mutation of the collagen gene.

Detection of mutated collagen in the injured organ was evidence that BM-derived cells secrete collagen and could contribute to fibrosis [36]. Furthermore, using dual immunofluorescence, collagen expressing fibrocytes can be easily discriminated from resident fibroblasts in human fibrotic lung [38].

3.3. Organ specific considerations of the BMs influence upon organ fibrosis

3.3.1. Lung disease

In allergic asthma in humans a population of cells were identified by Schmidt et al. as being fibrocytes (collagen I, CD34+); the authors went on to perform BM tracking experiments in a mouse model of allergic asthma and identified fibrocytes that were engrafting the lung from a circulating population. Furthermore, they were able to show in vitro that human circulating fibrocytes differentiated into a fibroblasts phenotype (αSMA+) in the presence of inflammatory cytokines [32,39]. In a murine model of obliterative bronchiolitis using heterotopic tracheal transplantation, circulating fibrocytes (CD45+, CXCR4+, collagen I+) engrafted the tracheal allograft and differentiated into fibroblasts. Through the use of an antibody to block the CXCL12 mediated fibrocyte migration a functional benefit was seen with less luminal obliteration and collagen deposition [40]. Fibrocytes have also been shown to traffic to the lungs following bleomycin challenge; both human fibrocytes in SCID mice and mouse fibrocytes in immune-competent mice [2,41]. Using BM transplant of GFP+ cells into WT mice CD45+/Col1+ GFP+ cells were found in the lungs following bleomycin challenge [2,41]. However Hashimoto and colleagues found no evidence that these cells differentiated into myofibroblasts and synthesised α-SMA. This may be due to incomplete repopulation of the BM following irradiation and transplant as a recent study showed that a small population of GFP− fibrocytes remained in the BM following lethal irradiation and transplant [42].

In fibrotic lung disease, the number of accumulating fibrocytes may be as much as 25% [42] and may significantly contribute to pulmonary fibrosis. Inhibition of the chemokine CXCl12 with a neutralising antibody reduced fibrocyte recruitment and lung fibrosis following bleomycin [2]. Moreover, elevated levels of circulating fibrocytes in peripheral blood in patients with idiopathic pulmonary fibrosis (IPF) correlate with poor prognosis [43] and are increased during acute exacerbations of the disease, whilst there was no elevation in fibrocyte numbers in patients with acute respiratory distress syndrome (ARDS) suggesting a specific role for these cells in idiopathic pulmonary fibrosis IPF [43] (Table 1). MSCs have been shown to home to the lung in response to fibrotic injury with bleomycin, and reduce inflammation and myofibroblast activation [21]. Whilst some studies show that these cells can incorporate into the airway epithelium and contribute to repair, other studies using a transgenic reporter mouse expressing GFP only in alveolar epithelial cells (surfactant protein C-GFP) argue against this being the case [44]. However, the injection of human umbilical vein MSCs has been shown to reduce fibrosis following bleomycin [45]. The role of MSCs and the potential for MSCs cell therapy in lung fibrosis therefore require further study.

3.3.2. Kidney fibrosis

Whilst the majority of scar forming cells in the kidney appeared to derive from endogenous pericytes [46], there also appears to be some contribution to fibrosis from circulating BM drive cells. Dual CD45+/type 1 collagen+ cells have been detected in the corticomedullary regions in ureteral ligation model of kidney fibrosis in mice [4]. Furthermore fibrocytes have been detected in human kidneys, CD45+/proCol1+ cells were seen in kidneys of patients with diabetic nephropathy and the numbers of cells in the interstitium correlated with the severity of tubulointerstitial lesions including interstitial fibrosis [47].

The functional significance of this route of fibrosis has been demonstrated using CXCL 16-knockout mice in a unilateral ureteral ligation model of renal fibrosis. Investigators found that compared with wild-type mice, CXCL16-knockout mice had significantly fewer BM-derived fibroblast precursors, together with fewer CD45-, collagen I-, and CXCR6-triple-positive fibroblast precursors in injured kidneys. This resulted in less renal myofibroblast activation and collagen deposition [48].

3.4. Liver fibrosis

Using BM transplantation from GFP positive donor mice into wild type recipients Baba et al. found that a proportion of stellate cells in the recipients liver were marked with the GFP transgene, suggesting that stellate cells may have the potential origin from BM [49]. Other investigators have also suggested in mice models of BM transplant with subsequent liver injury that both stellate cells and activated myofibroblasts may, at least in part, have a BM origin [36]. However other studies have suggested that hepatic stellate cells do not originate from the BM, and that the BM only contributes to a small number of collagen expressing cells in the liver following CCl_4 injury or following bile duct ligation in mice [35]. Using BM transplant from a collagen-alpha1(I)–luciferase (Col-Luc) transgenic mouse (which expresses which luciferase under the control of the collagen-alpha1(I) promoter) transplanted into lethally irradiated WT mice, it was shown that luciferase positive fibrocytes were recruited to the liver following CCL_4 induced liver injury [34]. Another study showed that BM-derived fibrocytes were recruited to the liver and differentiated into myofibroblasts an effect that was dependent on CCR1 [37]. Furthermore the investigators found little evidence of BM derived cells actually contributing to collagen transcription in the liver injury models. These contradictory results are certainly worthy of further investigation and in particular it may be worthy examining closely the role of the BM stromal cell population for the reasons outlined earlier as their contribution to any pro-fibrotic response may not read out in conventional adoptive transplant experiments.

In humans there has been a suggestion that a modest proportion (approximately 12%) of the myofibroblast like cells in the liver may have BM origin. This work was performed in two settings: (1) in male patients that had received female liver transplantation and then, to had biopsies for recurrent fibrosis; this suggested that a proportion of the myofibroblasts were marked with the liver recipients chromosomal markers (Y chromosome positive); this clearly did not prove BM origin but suggested a potential circulating source. Furthermore female patients have been analysed who have received male BM transplantation and then go on to develop liver injury; and again in this setting a proportion of the myofibroblasts contain the Y chromosome suggesting potential BM origin [32].

Towards the development of a potential cell therapy for liver fibrosis it was reported that transplantation of whole BMCs [50] and MSCs [51] reduces CCl_4-induced liver fibrosis in mice with decreased collagen production and increased MMP13 levels [51]. However

Table 1
Reported levels of fibrocytes and EPCs in human fibrotic disease.

Fibrocytes		
Normal	0.5% circulating leukocytes	[43]
IPF	20% circulating leukocytes	[43]
Asthma	3 fold increase compared to control	[83]
Scleroderma	2 fold increase compared to control	[9]
Hepatitis C	Up to50% circulating leukocytes	[84]
Decompensated cirrhosis	Up to 23.3% circulating leukocytes	[84]
EPCs		
COPD	40–60% increase	[85]
Cirrhosis	Increased from 0.01 to 0.1% leukocytes	[86]
IPF	7% of total lung cells	[87]
Asthma	1.7 fold increase circulating EPCs	[88]

The actual figures should be treated with caution and are not directly comparable as different methodologies are employed by individual groups.

this is an area with inconsistent results with other investigators finding no anti-fibrotic effect from MSC injection in models of liver fibrosis [52]. Furthermore MSCs themselves have been shown to adopt a myofibroblast phenotype in the liver. Di Bonzo et al. have shown that the injection of human MSCs into an immunodeficient mouse with liver injury resulted in the MSCs engrafting the liver and adopting a myofibroblast phenotype [53]. In addition another study has demonstrated whole BM to be pro-fibrotic following portal vein injection in mice, whereas purified fractions of BM derived macrophages resulted in a significant reduction the liver fibrosis [54]. However, a recent study has also shown that injection of autologous cultured bone marrow cells (comprising a mixture of macrophages and mesenchymal cells) improved liver function and liver fibrosis in mice [55]. Therefore, the specific bone marrow compartments contributing to reduced liver fibrosis after injection and therefore with potential as a therapy is still under debate. Clinical studies have reported improved liver function in cirrhotic patients following autologous bone marrow cell infusion therapy [56] and following infusion with umbilical cord MSCs [57,58], although these were not randomised controlled trials. Multicentre clinical trials are now underway and should inform this area in the near future [59] (Fig. 1).

3.5. Pancreatic fibrosis

Pancreatic fibrosis is a prominent feature of chronic pancreatitis (CP) and pancreatic cancer involving activated pancreatic stellate cells. Using irradiation and transplant of BM constitutively expressing enhanced green fluorescent protein (EGFP), one study showed that BM-derived cells accounted for 20.2% of α-smooth muscle actin-positive activated PSCs following induction of CP by repeated cerulein injections [60]. A second study in a mouse dietary model of pancreatitis revealed that the number of BM-derived activated pancreatic stellate cells rose during injury to 23.3 ± 0.9% of all activated pancreatic stellate cells which produced PDGF and TGFβ1 [61]. Interestingly the proportion of BM-derived cells then fell as the injury resolved. With reference to human tissue, Barth and co-workers showed that CD34+ fibrocytes and myofibroblasts could be detected in human chronic pancreatitis and ductal adenocarcinoma [62].

3.6. Skin fibrosis

There are a number of reports in mice suggesting that BM derived cells can engraft skin and produce cells of a fibroblast or myofibroblast phenotype [63]. However when the actual source of collagen production in skin was analysed in a mouse model of fibrogenesis and wound healing, using mice transplanted with a BM from EGFP-Col1 reporter mice, very little collagen transcription from the BM derived cells was shown to occur in the skin following dermal excision although a small number of CD45+/Col1+ cells (possibly fibrocytes) were found after subcutaneous injection of bleomycin [64]. Furthermore BM transplant experiments and parabiosis experiments using a collagen reporter GFP found no evidence of collagen producing BM derived cells in skin wounds with all GFP+ cells comprising inflammatory cells [65]. However there is mounting evidence that CD45+/Col1+ cells may contribute to fibrosis in nephrogenic fibrosing dermopathy [66–68] and following radiation [69].

3.6.1. Gut

Irradiation and BM transplant studies in mice have revealed that a proportion of the pericryptal myofibroblasts detected in the gut are derived from the BM. Using in situ hybridisation for the Y chromosome in female mice that have received irradiation, and transplant with male BM, frequent Y chromosome positive myofibroblasts were detected [70]. A follow on study of colitis confirmed that the BM cells were confined to the non-epithelial compartment and did not result in intestinal epithelial engraftment [71].

3.6.2. BM derived monocyte–macrophages

The BM derived macrophages have been shown to influence both the development and the recovery of fibrosis in several organs including the liver and lung. Murine models of carbon tetrachloride induced liver injury have been used to analyse the monocyte macrophages role in liver fibrosis. Using the CD11b-DTR mouse (which expresses the human diphtheria toxin receptor in cells of myeloid lineage) to conditionally delete macrophages it was shown that deletion of macrophages during hepatic injury reduced the *formation* of liver fibrosis; however deletion of macrophages during the recovery phase from the liver injury resulted in less *resolution* of the liver fibrosis [72]. Using BM cell tracking by sex mismatched BM transplantation it was shown that nearly half of the scar associated macrophages in the liver were indeed circulating from the BM [72]. The fact that macrophages may have an anti-fibrotic role in liver fibrosis has been exploited to develop macrophages as a cell therapy for liver fibrosis. Thomas and co-workers showed that a single intra-portal injection of macrophages was able to have a significant effect on the fibrosis and regeneration in the CCl4 model of chronic injury [54]. The macrophage injection had a profound effect upon the cell milieu in the hepatic scar area and induced recruitment of endogenous macrophages and neutrophils to the scar area. This cellular influx stimulated a regulation of matrix metalloproteinase that was able to induce apoptosis of hepatic my fibroblasts together with a reduction in hepatic collagen. Alongside this, macrophage injection induced a stimulation of the regenerative response in the damaged liver.

The function of macrophages in the progression of pulmonary fibrosis has been under debate for several years primarily due to the finding that human IPF is largely unresponsive to corticosteroids. However, recent published data suggest that this situation may be more complex than previously thought [73]. Using the bleomycin model it has been shown that lung macrophages can be the predominant source of TGF-β in the lung [74]. Furthermore, corticosteroids have been shown to support alternative macrophage activation and increase secretion of TGF-β [75]. Moreover, a recent study in patients who develop an accelerated form of fibrotic lung disease demonstrated that they have deregulated alveolar macrophages [76]. Gibbons and co-workers showed that alternatively activated macrophage expansion was stimulated by recruited Ly6Chi monocytes and could exacerbate fibrosis induced by bleomycin and adenoviral delivery of TGF in the mouse lung. Moreover, ablation of lung macrophages during fibrogenesis reduced the resulting lung fibrosis in these models [73]. This demonstrates a crucial role for macrophages in determining the severity of fibrotic lung injury and opens a novel area of investigation to identify new therapies to treat patients with IPF.

4. BM cells in the fibrotic response to cancers

BM cells particularly MSCs also contribute to the development of new tissue stroma and this has been widely studied in wound repair and in the lung; however tumour formation is also uniquely dependent on the surrounding stromal cells of the tumour microenvironment. The stroma contains resident structural cells (fibroblasts, epithelium and endothelium) and inflammatory cells which secrete growth factors that function to protect the developing tumour from immune attack. BM transplant experiments have shown that up to 40% of the myofibroblasts are BM-derived in murine studies [77]. There is an abundance of literature showing that MSCs specifically home to and incorporate into the tumour stroma in several malignancies including breast, lung and colorectal cancer (reviewed in Ref. [78]). However their function within the stroma is unclear. On one hand MSCs have been shown to be tumorigenic as they form the protective stroma and are anti-inflammatory and produce factors such as VEGF, TGF and IL-10 and indolamine dioxygenase which down regulate T cell function and promote angiogenesis. However there is also evidence that they can have anti-tumorigenic effects by down regulation of the wnt and Akt

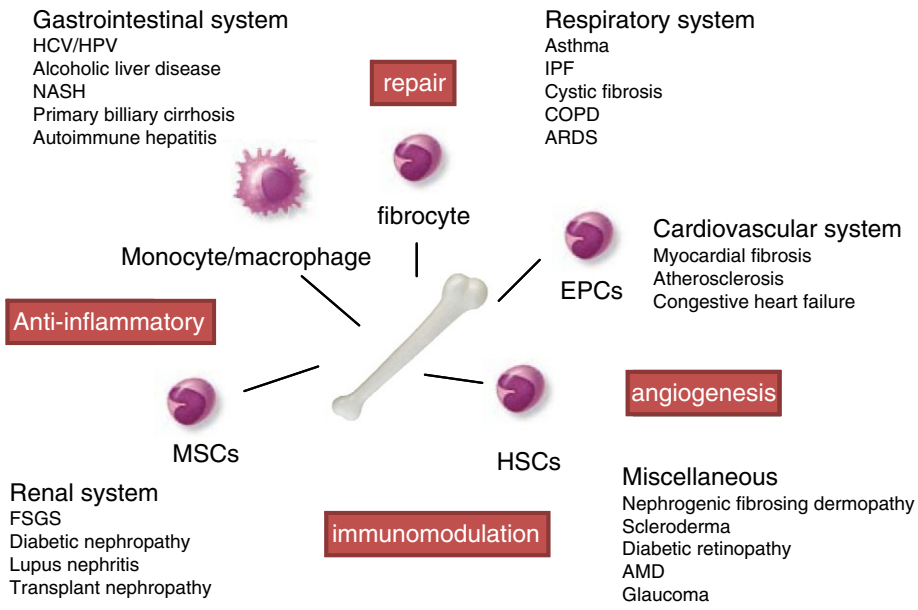

Fig. 1. Bone marrow cells involved in organ fibrosis and potential therapy.

pathways [79,80]. Probably the most interesting feature therapeutically is the use of MSCs as delivery vehicles for chemotherapy or cytotoxic drugs [79,81,82]. Exogenously delivered MSCs are a particularly attractive avenue for stem cell mediated cancer therapy, as unlike HSCs they can be given as cellular therapy as they can be rapidly expanded in vitro and do not pose the potential problems associated with irradiation and BM transplantation as they lack expression of MHC-II and co-stimulatory molecules. Approaches here have included MSCs expressing the apoptosis inducing TRAIL and IFNs [81].

5. Conclusions

The BM contribution to organ fibrosis is a particularly controversial area with many contradictory results using varying methodologies in different models. This makes broad conclusions particularly difficult; however, some can be drawn. There are a population of circulating fibrocytes that can engraft certain organs in conditions of inflammation and tissue damage and these cells are a likely source of collagen to some degree. Blocking their recruitment appears to have therapeutic benefit particularly in the setting of lung fibrosis. MSCs remain enigmatic despite years of study; there are many published results showing that their use in model of organ injury and fibrosis can resource injury, inflammation and fibrosis. Yet there are many negative studies also and even studies showing that the injected MSCS can adopt a scar forming phenotype. It will be worth considering whether their therapeutic use is justified based upon the organ, context, and chronicity of the injury and the experimental evidence available. Modern mouse transgenic technologies using collagen reports systems are bringing clarity to the field and have revealed that in certain settings there is little apparent collagen deposition from the BM in these models (e.g. skin). This field will grow and bring greater clarity to the field. The BM derived macrophages are important orchestrators of the fibrotic response and may have both pro and anti-fibrotic properties. BM derived macrophages may also have therapeutic role in organ fibrosis and should be studied further.

Within the BM there are population of stem cells including MSCs and HSCs. The progeny of HSCs including fibrocytes and monocytes can infiltrate inflamed organs and contribute to fibrosis either directly (fibrocytes) or through paracrine signalling to other scar forming cells locally (monocytes and their differentiated form macrophages). Stromal progenitor cells may mobilise from the BM in certain conditions. In the recovery from injury and fibrosis macrophages can orchestrate and directly aid the resolution of fibrosis. MSCs can have anti-inflammatory and anti-fibrotic effects in some models of organ fibrosis; however they may directly from myofibroblast-like cells also. Macrophages may have some therapeutic potential in cell therapy.

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